General

Guideline Title

Evidence-based guideline: treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.

Bibliographic Source(s)

Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D. Evidence-based guideline: treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17;76(20):1758-65. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in November 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

In Patients with Painful Diabetic Neuropathy (PDN), What Is the Efficacy of Pharmacologic Agents to Reduce Pain and Improve Physical Function and Quality of Life (QOL)?

Anticonvulsants

Conclusions

Based on consistent Class I evidence, pregabalin is established as effective in lessening the pain of PDN. Pregabalin also improves QOL and lessens sleep interference, though the effect size is small. Based on one Class I study, gabapentin is probably effective in lessening the pain of PDN. Based on 2 Class II studies, sodium valproate is probably effective in treating PDN. Lamotrigine is probably not effective in treating PDN. Based on Class II evidence, oxcarbazepine is probably not effective in treating PDN. There is conflicting Class III evidence for the effectiveness of topiramate in treating PDN. Based on Class III evidence, lacosamide is possibly not effective in treating PDN. The degree of pain relief afforded by anticonvulsant agents is not associated with improved physical function.

Recommendations

1. If clinically appropriate, pregabalin should be offered for the treatment of PDN (Level A).
2. Gabapentin and sodium valproate should be considered for the treatment of PDN (Level B).
3. There is insufficient evidence to support or refute the use of topiramate for the treatment of PDN (Level U).
4. Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for the treatment of PDN (Level B).

Clinical Context

Although sodium valproate may be effective in treating PDN, it is potentially teratogenic and should be avoided in diabetic women of childbearing age. Due to potential adverse effects such as weight gain and potential worsening of glycemic control, this drug is unlikely to be the first treatment choice for PDN.

Antidepressants

Conclusions

Based on 3 Class I and 5 Class II studies, the antidepressants amitriptyline, venlafaxine, and duloxetine are probably effective in lessening the pain of PDN. Venlafaxine and duloxetine also improve QOL. Venlafaxine is superior to placebo in relieving pain when added to gabapentin. There is insufficient evidence to determine whether desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine are effective for the treatment of PDN.

Recommendations

1. Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of PDN (Level B). Data are insufficient to recommend one of these agents over the others.
2. Venlafaxine may be added to gabapentin for a better response (Level C).
3. There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of PDN (Level U).

Opioids

Conclusions

Based on one Class I study, dextromethorphan is probably effective in lessening the pain of PDN and improving QOL. Based on Class II evidence, morphine sulfate, tramadol, and oxycodone controlled release are probably effective in lessening the pain of PDN. Dextromethorphan, tramadol, and oxycodone controlled-release have moderate effect sizes, reducing pain by 27% compared with placebo.

Recommendations

Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for the treatment of PDN (Level B). Data are insufficient to

recommend one agent over the other.

Clinical Context

The use of opioids for chronic nonmalignant pain has gained credence over the last decade due to the studies reviewed in this article. Both tramadol and dextromethorphan were associated with substantial adverse events (e.g., sedation in 18% on tramadol and 58% on dextromethorphan, nausea in 23% on tramadol, and constipation in 21% on tramadol). The use of opioids can be associated with the development of novel pain syndromes such as rebound headache. Chronic use of opioids leads to tolerance and frequent escalation of dose.

Other Pharmacologic Agents

Conclusions

Based on Class I and Class II evidence, capsaicin cream is probably effective in lessening the pain of PDN. Based on Class III studies, there is insufficient evidence to determine if intravenous lidocaine is effective in lessening the pain of PDN. Based on Class III evidence, the Lidoderm patch is possibly effective in lessening the pain of PDN. Based on Class I evidence, clonidine and pentoxifylline are probably not effective for the treatment of PDN. The evidence for the effectiveness of mexiletine is contradictory; however, the only Class I study of this agent indicates that mexiletine is probably ineffective for the treatment of PDN. There is insufficient evidence to determine whether vitamins and α-lipoic acid are effective for the treatment of PDN. Based on Class I evidence, isosorbide dinitrate spray is probably effective for the treatment of PDN.

Recommendations

1. Capsaicin and isosorbide dinitrate spray should be considered for the treatment of PDN (Level B).
2. Clonidine, pentoxifylline, and mexiletine should probably not be considered for the treatment of PDN (Level B).
3. The Lidoderm patch may be considered for the treatment of PDN (Level C).
4. There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid in the treatment of PDN (Level U).

Clinical Context

Although capsaicin has been effective in reducing pain in PDN clinical trials, many patients are intolerant of the side effects, mainly burning pain on contact with warm/hot water or in hot weather.

<u>In Patients with PDN, What Is the Efficacy of Nonpharmacologic Modalities to Reduce Pain and Improve Physical Function and QOL?</u>

Electrical Stimulation, Magnetic Field Treatment, Other Interventions

Conclusion

Based on a Class I study, electrical stimulation is probably effective in lessening the pain of PDN and improving QOL. Based on single Class I studies, electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy are probably not effective for the treatment of PDN. There is not enough evidence to support or exclude a benefit of amitriptyline plus electrotherapy in treating PDN.

Recommendations

1. Percutaneous electrical nerve stimulation should be considered for the treatment of PDN (Level B).
2. Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for the treatment of PDN (Level B).
3. Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment of PDN (Level U).

<u>Definitions</u>:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Painful diabetic neuropathy

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Endocrinology

Internal Medicine

Neurology

Physical Medicine and Rehabilitation

Intended Users

Physicians

Guideline Objective(s)

To develop a scientifically sound and clinically relevant evidence-based guideline for the treatment of painful diabetic neuropathy (PDN)

Target Population

Patients with painful diabetic neuropathy

Interventions and Practices Considered

1. Anticonvulsants
    - Pregabalin
    - Gabapentin
    - Sodium valproate
2. Antidepressants
    - Amitriptyline
    - Venlafaxine
    - Duloxetine
    - Venlafaxine in combination with gabapentin
3. Opioids
    - Dextromethorphan
    - Morphine sulfate
    - Tramadol
    - Oxycodone
4. Other pharmacologic agents
    - Capsaicin
    - Isosorbide dinitrate spray
    - Lidoderm patch
5. Other interventions
    - Percutaneous electrical nerve stimulation

Note: Topiramate, oxcarbazepine, lamotrigine, lacosamide, desipramine, imipramine, fluoxetine, the combination of nortriptyline and fluphenazine, clonidine, pentoxifylline, mexiletine, vitamins, α-lipoic acid, amitriptyline plus electrotherapy, electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy were considered but not recommended.

Major Outcomes Considered

- Pain reduction

- Improvement in physical function
- Quality of life
- Adverse events associated with treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2011 Guideline

In August 2008, a literature search of MEDLINE and EMBASE was performed in all languages using the MeSH term diabetic neuropathies and its text word synonyms and key words for the therapeutic interventions of interest.

Search Terms Used

Painful diabetic neuropathy OR neuropathic pain OR diabetes AND: Anticonvulsant, anti-epileptic, anti-depressant, anti-arrhythmic, spinal cord stimulation, infra-red therapy, acupuncture, opioids, topical patches, lidocaine, intra-thecal baclofen, TENS, vitamins, life-style modification, metabolic control, baclofen.

The search identified 2,234 citations, the titles and abstracts of which were reviewed by at least 2 authors for relevance.

2016 Reaffirmation

The guideline developer searched Medline for studies published between January 2013 to April 2014, using the following search strategy: Painful diabetic neuropathy OR neuropathic pain OR diabetes AND: Anticonvulsant, anti-epileptic, anti-depressant, anti-arrthymic, spinal cord stimulation, infra-red therapy, acupuncture, opioids, topical patches, lidocaine, intra-thecal baclofen, TENS, vitamins, life-style modification, metabolic control, baclofen. Inclusion criteria were humans only, relevant to clinical questions; exclusion criteria used to screen search results were the same as described in the 2011 published guideline.

Number of Source Documents

The search identified 2,234 citations, the titles and abstracts of which were reviewed by at least 2 authors for relevance, resulting in 463 articles. All of these articles were reviewed in their entirety, and of these, the panel identified 79 relevant articles.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined

d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Each article was rated by at least 2 authors according to the American Academy of Neurology (AAN) criteria for the classification of therapeutic articles (see the "Rating Scheme for the Strength of the Evidence" field), and recommendations were linked to the strength of evidence (see the "Rating Scheme for the Strength of the Recommendations" field) and to effect size of the intervention. Disagreements regarding classification were arbitrated by a third reviewer.

Articles were included if they dealt with the treatment of painful diabetic neuropathy (PDN), described the intervention clearly, reported the completion rate of the study, and defined the outcome measures clearly. The panel also considered the side effects of the treatment and measures of function and quality of life (QOL), if any. Case reports and review articles were excluded.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2011 Guideline

In January 2007, the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation convened an expert panel from the United States and Canada, selected to represent a broad range of relevant expertise.

Recommendations were linked to the strength of evidence using the scheme described in the "Rating Scheme for the Strength of the Evidence" field, and to effect size of the intervention.

2016 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) Subcommittee member who had expertise in neuropathies conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were NOT met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists. This guideline is currently considered outdated, and will be retired following publication of an updated guideline. This guideline update project has been approved and is on the GDDI's waitlist; it has not yet been initiated. However, as there are no safety concerns with the content of this guideline and no other guidance exists on the topic, this guideline will retain a current status until publication of the updated guideline.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, Neurology® peer reviewers, and representatives from related fields.

The guideline was approved by the AAN Quality Standards Subcommittee on November 13, 2010; by the AAN Practice Committee on December 15, 2010; by the AAN Board of Directors on February 10, 2011; by the Neuromuscular Guidelines Steering Committee on October 8, 2010; by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Practice Issues Review Panel on January 15, 2011; by the AANEM Board of Directors on February 15, 2011; by the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Quality Practice & Policy Committee on February 6, 2011; and by the AAPM&R Board of Governors on March 11, 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of patients with painful diabetic neuropathy to reduce pain and improve physical function and quality of life

Potential Harms

- Although sodium valproate may be effective in treating painful diabetic neuropathy (PDN), it is potentially teratogenic and should be avoided in diabetic women of childbearing age. Due to potential adverse effects such as weight gain and potential worsening of glycemic control, this drug is unlikely to be the first treatment choice for PDN.
- Both tramadol and dextromethorphan were associated with substantial adverse events (e.g., sedation in 18% on tramadol and 58% on dextromethorphan, nausea in 23% on tramadol, and constipation in 21% on tramadol). The use of opioids can be associated with the development of novel pain syndromes such as rebound headache. Chronic use of opioids leads to tolerance and frequent escalation of dose.
- Although capsaicin has been effective in reducing pain in PDN clinical trials, many patients are intolerant of the side effects, mainly burning pain on contact with warm/hot water or in hot weather.

Contraindications

Contraindications

Sodium valproate is potentially teratogenic and should be avoided in diabetic women of childbearing age.

Qualifying Statements

Qualifying Statements

- This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.
- It is notable that the placebo effect varied from 0% to 50% pain reduction in the reported studies. Adjuvant analgesic agents are drugs primarily developed for an indication other than treatment of painful diabetic neuropathy (PDN) (e.g., anticonvulsants and antidepressants) that have been found to lessen pain when given to patients with PDN. Their use in the treatment of PDN is common. The panel recognizes that PDN is a chronic disease and that there are no data on the efficacy of the chronic use of any treatment, as most trials have durations of 2–20 weeks. It is important to note that the evidence is limited, the degree of effectiveness can be minor, the side effects can be intolerable, the impact on improving physical function is limited, and the cost is high, particularly for novel agents.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D. Evidence-based guideline: treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17;76(20):1758-65. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 May 17 (reaffirmed 2016 Nov 22)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology (AAN)

Guideline Committee

Quality Standards Subcommittee (QSS)

Composition of Group That Authored the Guideline

Guideline Authors: V. Bril, MD, FRCP(C); J. England, MD, FAAN; G.M. Franklin, MD, MPH, FAAN; M. Backonja, MD; J. Cohen, MD, FAAN; D. Del Toro, MD; E. Feldman, MD, PhD, FAAN; D.J. Iverson, MD, FAAN; B. Perkins, MD, FRCP(C), MPH; J.W. Russell, MD, MS, FRPC; D. Zochodne, MD

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Financial Disclosures/Conflicts of Interest

Dr. Bril has received research support from Talecris Biotherapeutics, Eisai Inc., Pfizer Inc, Eli Lilly and Company, and Johnson & Johnson. Dr. England serves on the speakers' bureau for and has received funding for travel or speaker honoraria from Talecris Biotherapeutics and Teva Pharmaceutical Industries Ltd.; served as an Associate Editor for *Current Treatment Options in Neurology*; receives research support from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS), Wyeth, AstraZeneca, and Pfizer Inc; holds stock/stock options in Wyeth and Talecris Biotherapeutics; and has served as an expert witness in a medico-legal case. Dr. Franklin serves on the editorial board of *Neuroepidemiology*; serves as a consultant for the New Zealand Accident Fund; and serves as a consultant for the Workers Compensation Research Institute. Dr. Backonja served on a Safety Monitoring Board for Medtronic, Inc.; serves on the editorial boards of *Clinical Journal of Pain*, *European Journal of Pain*, *Journal of Pain*, *Pain*, and *Pain Medicine*; is listed as author on a patent re: A hand-held probe for suprathreshold thermal testing in patients with neuropathic pain and other neurological sensory disorders; serves as a consultant for Allergan, Inc., Astellas Pharma Inc., Eli Lilly and Company, Medtronic, Inc., Merck Serono, NeurogesX, Pfizer Inc, and SK Laboratories, Inc.; and receives research support from NeurogesX. Dr. Cohen serves on an FDA Peripheral and Central Nervous System Drugs Advisory Committee; receives publishing royalties for *What Would You Do Now? Neuromuscular Disease* (Oxford University Press, 2009); estimates that he performs clinical neurophysiology testing as 50% of his clinical practice; and has given expert testimony, prepared an affidavit, and acted as a witness in a legal proceeding with regard to vaccine-related injuries and peripheral nerve injuries. Dr. Del Toro receives research support from the NIH. Dr. Feldman serves on a Data Safety and Monitoring Board for Novartis; serves on the editorial boards of *Annals of Neurology* and the *Journal of the Peripheral Nervous System*; receives publishing royalties from UpToDate; and receives research support from the NIH, the Taubman Research Institute, and the American Diabetes Association. Dr. Iverson serves as editor of *NeuroPI* and has been a treating expert witness with regard to a legal proceeding. Dr. Perkins has received research support from Medtronic, Inc., the Canadian Institutes of Health Research, the Juvenile Diabetes Research Foundation, and the Canadian Diabetes Association. Dr. Russell has received honoraria from Exelixis Inc. and Baxter International Inc.; and receives research support from Baxter International Inc., the NIH, the US Veterans Administration, the American Diabetes Association, and the Juvenile Diabetes Foundation. Dr. Zochodne serves on a scientific advisory board for and holds stock options in Aegera Therapeutics Inc.; has received honoraria from Ono Pharmaceutical Co. Ltd.; receives publishing royalties for *Neurobiology of Peripheral Nerve Regeneration* (Cambridge University Press, 2008); has received research support from the Canadian Institutes of Health Research, the Canadian Diabetes Association, the Juvenile Diabetes Research Foundation, the National Science and Engineering Research Council, the NIH, and the Alberta Heritage Foundation for Medical Research, Baxter International Inc., and Aegera Therapeutics Inc.; and has served as a co-PI on industry trials with Valeant Pharmaceuticals International and Pfizer Inc.

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in November 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Availability of Companion Documents

The following are available:

- Treatment of painful diabetic neuropathy. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2011. 2 p. Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site.
- Treatment of painful diabetic neuropathy. Case presentation. St. Paul (MN): American Academy of Neurology. 2011. 8 p. Available in Portable Document Format (PDF) from the AAN Web site.
- Treatment of painful diabetic neuropathy. Slide presentation. St. Paul (MN): American Academy of Neurology. 2011. 50 p. Available from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site.

Patient Resources

The following is available:

- Treatment of painful diabetic neuropathy. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology. 2011. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on August 24, 2011. This summary was updated by ECRI Institute on July 10, 2013 following the U.S. Food and Drug Administration advisory on Valproate. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines. The currency of the guideline was reaffirmed by the developer in November 2016 and this summary was updated by ECRI Institute on January 30, 2017.

Copyright Statement

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